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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,583	POUWELS ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/01/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 30-49* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 30-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 43-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on amendment of December 1, 2003 has been entered. Claim 29 is cancelled. Claims 28 and 43 are amended. New claims 43-49 are added. Claims 1-28 and 30-49 are pending. Claims 1-27 and 30-42 are withdrawn from considertion by examiner as drawn to the non-elected invention. Claims 28, and 43-49 are the subject of this Office Action.

Detailed Office Action

1. Objections

Objection to claim 43 (inadvertently numbered by Applicants as claim 39) made in the previous Office Action is withdrawn because the claim has been amended.

2. Rejections

2.1. 35 USC, section 112, second paragraph

The amended claim 28 and claims 43-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 reads:

"Claim 28: A process for the production of vitamin B_{12} (cobalamin), the process comprising culturing a *Propionibacterium* host cell under conditions in which the vitamin is produced and, if necessary, isolating the vitamin, wherein the *Propionibacterium* host cell contains a polynucleotide comprising a sequence that is:

(a) SEQ ID NO:1 or the complement thereof;

(b) a sequence from SEQ ID NO: 1 that corresponds to either the 1.7. kb fragment of SEQ ID NO:1 delineated by restriction sites Sal1 and AlwNI or nucleotides 1 to 1800 of SEQ ID NO:1; or

(c) a sequence that is at least 70% homologous to a sequence as defined under (a) or (b) over a region of at least 100 contiguous nucleotides and which retains the ability to autonomously replicate in *Propionibacterium*;

and a sequence that is an endogenous gene of a *Propionibacterium* involved in vitamin B_{12} biosynthesis operatively linked to a control sequence which is capable of providing for expression of the gene."

The form of the claim is improper, because its alternative form is confusing. It is unclear whether the host cell should contain a polynucleotide of SEQ ID NO:1 (or its complement) **and** a sequence from SEQ ID NO: 1 that corresponds to either the 1.7. kb fragment of SEQ ID NO:1 delineated by restriction sites Sal1 and AlwNI or nucleotides 1 to 1800 of SEQ ID NO:1 **or**

the polynucleotide that contain a sequence that is at least 70% homologous to a sequence as defined under (a) or (b) over a region of at least 100 contiguous nucleotides and which retains the ability to autonomously replicate in *Propionibacterium* **and** a sequence that is an endogenous gene of a *Propionibacterium* involved in vitamin B_{12} biosynthesis operatively linked to a control sequence which is capable of providing for expression of the gene.

If the claim is intended to be in the form of a Markush group the proper language is "a sequence from the group of:

(a) SEQ ID NO:1 or the complement thereof;

(b) a sequence from SEQ ID NO: 1 that corresponds to either the 1.7. kb fragment of SEQ ID NO:1 delineated by restriction sites Sal1 and AlwNI or nucleotides 1 to 1800 of SEQ ID NO:1;

(c) a sequence that is at least 70% homologous to a sequence as defined under (a) or (b) over a region of at least 100 contiguous nucleotides and which retains the ability to autonomously replicate in *Propionibacterium*; and

(d) a sequence that is an endogenous gene of a *Propionibacterium* involved in vitamin B_{12} biosynthesis operatively linked to a control sequence which is capable of providing for expression of the gene."

However, the polynucleotide (d) is generic and the genus mostly comprises the species that do no share structural and functional similarities with sequences (a), (b) and (c). Thus including sequence (d) into the Markuch group would be improper.

In addition, the claim recites the phrase "involved in the production of vitamin B_{12}", which is vague and confusing and not defined by the claim or by the specification. This phrase renders the claim indefinite. The number of genes that are "involved" in production of any chemical substance by the cell is large, starting with the genes encoding any tRNA necessary in synthesis of any protein (enzyme) catalyzing the steps of said production.

The examiner suggests the following language: "gene of *Propionibacterium* belonging to vitamin B_{12} biosynthesis pathway".

Furthermore, claim 28 is directed to production of vitamin B_{12} by *Propionibacterium* having a plasmid comprising an origin of replication in SEQ ID NO: 1 or its fragment contained between SalI and AlwNI restriction sites (nucleotides 1 - 1800 of SEQ ID NO: 1); part a) and of the claim. However, the claim is confusing in recitation of DNA fragment c) that has no ability to originate replication, because it does not contain the replication origin of the p545 plasmid. Thus, DNA fragments c) cannot be maintained within *Propionibacterium*.

2.2. 35 USC, section 112, first paragraph

2.2.2. Lack of written description

Claim 28 and 43-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 28 is directed to a genus of processes for production of vitamin B_{12} (cobalamin), comprising culturing a *Propionibacterium* host cell containing a polynucleotide comprising a sequence that is:

(a) SEQ ID NO:1 or the complement thereof;

(b) a sequence from SEQ ID NO: 1 that corresponds to either the 1.7. kb fragment of SEQ ID NO:1 delineated by restriction sites Sal1 and AlwNI or nucleotides 1 to 1800 of SEQ ID NO:1; or

(c) a sequence that is at least 70% homologous to a sequence as defined under (a) or (b) over a region of at least 100 contiguous nucleotides and which retains the ability to autonomously replicate in *Propionibacterium*;

and a sequence that is an endogenous gene of a *Propionibacterium* involved in vitamin B_{12} biosynthesis operatively linked to a control sequence which is capable of providing for expression of the gene."

The specification is silent about the structure of any polypeptide that is 70% homologous to sequences (a) or (b) over a region of at least 100 contiguous nucleotides and which retains the ability to autonomously replicate in *Propionibacterium.* Also, Applicants failed to disclose any fragment of SEQ ID NO:1 or variants thereof which is capable of providing for expression of an endogenous gene within *Propionibacterium*, wherein the sequence is other than that of SEQ ID NO: 1 or its fragment consisting of nucleotides 1-1800. The Applicants write, "...endogenous gene may be inserted

between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of SEQ ID NO: 1 [complete nucleotide sequence of the p545 plasmid, MW]"(page 10, line 22). Therefore, they used in construction of their plasmid pBRES36COB nucleotides 1-1800 of SEQ ID NO: 1 containing p545 plasmid replication origin and the *cobA* (uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii*. Applicants did not link operationally the cobA, or other gene, to any other replication origin than the fragment of SEQ ID NO: 1. The specification does not contain any disclosure of the function of all plasmids within the genus of claimed method, and the vast majority of such plasmids would be unable to encode a vitamin B_{12} biosynthetic gene as they lack any functional replication origin and thus would be lost on growth of the bacterial culture. As many functionally unrelated plasmids are recited in the claimed methods, the single disclosed plasmid is not representative of the genus of plasmids within the claimed methods. Therefore, one cannot reasonably conclude that Applicants had possession of the of the attributes and features of all claimed methods.

In their response, on page 19 line 12 Applicants traverse this rejection arguing,

> "The specification exemplifies use of a polynucleotide with the sequence of SEQ ID NO:1 in particular nucleotides 1-1800 of SEQ ID NO:1. The specification also envisages and teaches homologous variants of those sequences (for example, at page 4, lines 14-17) and specifies that those variants may maintain the

capability to autonomously replicate in *Propionibacteria* (for example, at page 8, lines 9 to 12). Once provided with the sequence of SEQ ID NO:1, its function and specification, it is a relatively simple matter for a skilled person to create or identify homologous sequences as claimed which nevertheless retain replicative function."

Applicants arguments have been fully considered but are found not persuasive.

On page 4, lines 14-17 of the specification Applicants write:

"Polynucleotides included in the invention can be generally at least 70%, preferably at least 0 or 90%, more preferably at least 95%, and optimally at least 98% homologous (to the sequences (a) to (d)) [SEQ ID NO:1 or the complement thereof, a sequence from the 3.6 kb plasmid of *Propionibacterium freudenreichii* CBS101022, a sequence from the 3.6 kb plasmid of *Propionibacterium freudenreichii* CBS101023, a sequence that encodes a polypeptide of the invention such as at least part of)the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3, or complement thereof. See page 2, line 4-11.] over the region of at least 20, preferably a least 30, for instance at least 40, 60, or 100 or more contiguous nucleotides."

On page 8, lines 9-12 of the specification Applicants write:

> "Polynuclotides of the invention include variants of the sequence of SEQ ID NO:1 or of either 3.6 kb plasmid which are capable of autonomously replicatior remaining extrachromosomally in a host cell. Such variants may be stable in a bacterium such as a *Propionibacterium.*"

None of the passages quoted by Applicants in their traverse provides identifying structural characteristics of the claimed polynucleotides. The passages provide only description of genera of polynucleotides of the invention. The specification does not contain any disclosure of the function and structure of all the polynucleotides sequences derived from SEQ ID NO:1 by substitution, deletion or addition nucleotides so that the sequence that is at least 70% homologous to a sequence as defined under (a) or (b), in claim 28, over a region of at least 100 contiguous nucleotides and retains the ability to autonomously replicate in *Propionibacterium.*

Thus, predictability of the function of the representatives of the claimed genus of sequences that are at least 70% homologous to a sequence as defined under (a) or (b), in claim 28, over a region of at least 100 contiguous nucleotides is not apparent. Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would

recognize Applicants were in possession of the claimed invention when the application was filed and the rejection is maintned.

Applicants arguments "Once provided with the sequence of SEQ ID NO:1, its function and specification, it is a relatively simple matter for a skilled person to create or identify homologous sequences as claimed which nevertheless retain replicative function." refers to the question of enablement and not written description. However, if creating or identifying homologous sequences, as claimed, is a relatively simple matter, why Applicants themselves do not disclose any structure of polynucleotide that is at least 70% homologous to a sequence as defined under (a) or (b), in claim 28, over a region of at least 100 contiguous nucleotides and retains replicative function?

3.3.4. Scope of enablement

Claim 28 and 43-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of production of vitamin B_{12} by *Propionibacterium* cells transformed with the pBRES36COB vector or with p545 plasmid wherein cobA gene is inserted between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of said plasmid, does not reasonably provide enablement for a method when *Propionibacterium* cells are transformed with a polynucleotide comprising a sequence that is at least 70% homologous to a sequence as defined in parts (a) or (b) of claim 28, over a region of at least 100 contiguous nucleotides and which retains the

ability to autonomously replicate in *Propionibacterium* and a sequence that is an endogenous gene of a *Propionibacterium* involved in vitamin B_{12} biosynthesis operatively linked to a control sequence which is capable of providing for expression of the gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claim is not in accordance with the scope of enablement; see the above rejection for lack of written description. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses production of vitamin B_{12} by culturing *Propionibacterium* containing any sequence from natural and/or man-made source, wherein the sequence comprises:

(1) any sequence that is at least 70% homologous to SEQ ID NO: 1 or complement thereof or the sequence that corresponds to either the 1.7 kb fragment of SEQ ID NO: 1 delineated by restriction sites Sal 1 and AlwN1

or nucleotides 1-1800 of SEQ ID NO: 1,or complement thereof, over a region of at least 100 contiguous nucleotides or

(2) a gene of *Propionibacterium* involved in the production of vitamin B_{12} operatively linked to a control sequence, which is capable of providing for expression of the gene.

The specification provides an enablement (Example 5) how to produce vitamin B_{12} by culturing *Propionibacterium freudenreichii* ATCC6207 transformed with the vector named pBRES36COB containing p545 plasmid sequence controlling replication, and the *cobA* (uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii.* Thus, the scope of claim is limited to transformants of *Propionibacterium* that contains the *cobA* or other gene of vitamin B_{12} biosynthetic pathway operably linked to replication controlling element from plasmid p545. The specification is lacking any teaching of an origin of replication within a sequence that is at least 70% homologous over a region of at least 100 contiguous nucleotides of SEQ ID NO:1, or nucleotides 1-1800 of SEQ ID NO: 1or their complements. Futhermore, Applicants have failed to define what are the necessary structural features of nucleotides 1-1800 of SEQ ID NO: 1 that provide for its activity as an origin of replication in *Propionibacterium.*

Applicants failed to disclose a sequence of *Propionibacterium,* which is capable of providing for replication of an endogenous gene within *Propionibacterium*, wherein the sequence is other than that of SEQ ID NO: 1 or its fragment consisting of nucleotides 1-1800. The Applicants write, "...endogenous gene may be inserted between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of SEQ ID NO: 1 [complete nucleotide

sequence of the p545 plasmid, MW]"(page 10, line 22). Therefore, they used in construction of their plasmid pBRES36COB nucleotides 1-1800 of SEQ ID NO: 1 containing p545 plasmid replication origin and the *cobA* (uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii.* Applicants did not link operationally the cobA, or other gene, to any other replication origin than the fragment of SEQ ID NO:1.

The specification does not give examples or guidance as to the structure of replication origin that would be suitable for replicating and contained in any sequence that is at least 70% homologous to SEQ ID NO: 1 or complement thereof or the sequence that corresponds to either the 1.7 kb fragment of SEQ ID NO: 1 delineated by restriction sites Sal 1 and AlwN1 or nucleotides 1-1800 of SEQ ID NO: 1or complement thereof over a region of at least 100 contiguous nucleotides, and thus could be linked to one or more vitamin B_{12} biosynthesis genes to provide for vitamin B_{12} production.

Without further guidance as to the structure of the replication origin that may be used, probability of success in making the claimed invention is very low, and the experimentation left to those skilled in the art improperly extensive and undue.

3. Conclusion

No claim is in conditions for allowance, but claim 28 contains allowable subject matter for reasons indicated in the Office Action mailed to the Applicants on Dec. 3, 2002.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

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